Review

Tuberculosis as the Cause of Fever of Unknown Origin: A Review

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ABSTRACT

All reported series of fever of unknown origin were reviewed to determine the frequency of tuberculosis as the final diagnosis in this syndrome. Thirty-seven series from 1930 to 1995 were identified, comprising 3056 patients. Tuberculosis accounted for 7.9% of all diagnoses. Although methods of diagnoses changed over the period reviewed, rates of tuberculosis were relatively stable. Of 1366 patients with specific information regarding site of tuberculosis, extrapulmonary tuberculosis accounted for 4.8% of all cases and pulmonary tuberculosis 2.3%. Tuberculosis continues to be the final diagnosis in a significant proportion of patients with fever of unknown origin. Consideration should be given to empirical antituberculous therapy in persons with fever of unknown origin and a thorough but unrevealing workup.

Key Words: *diagnosis, fever of unknown origin, obscure, tuberculosis*

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Fever of unknown origin (FUO) is a classic syndrome that has fascinated physicians since at least the 1930s.[1-9] In 1961, Petersdorf and Beeson reported on 100 cases and standardized the definition of FUO for subsequent investigators[10]: at least 3 weeks of unexplained fever that has not been diagnosed despite extensive evaluation. Since then, at least 27 additional series with details of final diagnoses have been reported.[11-37] In most series, the vast majority of diagnoses are accounted for by one of the "Big Three": infection, cancer, and collagen vascular disease.[13]

Tuberculosis is the single most common infectious cause of FUO in many of these series. Although "classic" tuberculosis is often simple to diagnose, the difficulties in diagnosing tuberculosis in certain patients are legion. Many physicians have experienced the humbling call from the microbiology laboratory notifying them that tissue samples of a patient, perhaps already discharged or deceased, are growing *Mycobacterium tuberculosis* in culture. This diagnostic difficulty appears heightened in patients infected with human immunodeficiency virus (HIV), since numerous other opportunistic infections may present with similar symptoms.

To determine whether the rate of tuberculosis as a cause of FUO has changed over time, varies by country, or differs according to host population, all reported series of FUO were reviewed. The wisdom of giving a trial of empirical antituberculous therapy to such patients in light of these results is considered.

METHODS

Using MEDLINE, the English language literature since 1966 was searched for "fever of unknown origin." Additional reports were identified by reviewing the bibliographies of these articles. Reports that did not include specific numbers of patients or specific diagnoses were excluded.

RESULTS

Thirty-seven studies with specific information regarding final diagnoses were identified, including reports from North and South America, Asia, Africa, and Europe. Nine reports predated the Petersdorf and Beeson series (Table 1), including the article by Alt and Barker.[1] Twenty reports in adults that adhered to the Petersdorf and Beeson definition of FUO were identified (Table 2), and eight series reported outcome in specific hosts, including those with HIV infection, the elderly, and the young (Table 3).

The 37 series comprised 3056 patients. Two often-cited series,[13,18] accounting for 350 patients, did not give specific information about tuberculosis and are excluded from further analysis. In addition, three other studies did not give sufficient information about etiologies other than tuberculosis and are considered only when cases of tuberculosis are analyzed.[12,20,28] Of the 2509 patients with

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Table 1. Studies Reported Prior to Petersdorf-Beeson Definition of FUO (n = 9)

Author	Fever Duration	Hospital Location	Study Period	Total Cases	Diagnosis %*				Tuberculosis†	
					Inf	CA	CVD	Unk	Number (%)	Type
Alt & Barker[1]	>10 d	Boston	1913–29	57	16	11	0	63	5 (9)	2 P 3 EP
Kinter & Rowntree[2]	1 mo	Mayo Clinic	1919–30	100	35	N/A	N/A	65	0 (0)	0 P 0 EP
Keefer[3]	months	Boston City	1931–39	80	64	21	0	0	8 (10)	0 P 8 EP
Hamman & Walnwright[4]	wk–mo‡	Johns Hopkins	1930s	36	19	6	0	75	2 (6)	2 P 0 EP
Hamman & Wainwright[5]	wk–mo§	Johns Hopkins	1930s	54	59	22	0	19	9 (17)	N/A P N/A EP
Bottiger[6]	>10 d	Karolinska	1940–49	68	16	10	4	69	4 (6)	1 P 3 EP
Pettersson[7]	>6 d	Finland	1950–59	83	18	6	6	67	9 (11)	7 P 2 EP
Geraci et al[8]	>2 wk	Mayo Clinic¶	?–1959	70	21	30	1	20	5 (7)	0 P 5 EP
Fransen & Bottiger[9]	2 wk	Stockholm	1960	60	12	32	7	45	5 (8)	1 P 4 EP

*Does not include patients with "Other" diagnoses (e.g., drug fever, factitious fever, pulmonary embolus, etc.); †included in "Infection" diagnosis group (P = pulmonary; EP = extrapulmonary); ‡low-grade fever; §high-grade fever; ¶all patients underwent laparoscopy.
Inf = infection; CA = cancer; CVD = collagen vascular disease, Unk = unknown; N/A = not available.

complete information, infection was the diagnosis in 37%, cancer in 15%, and collagen vascular disease in 10%. These rates approximate those reported by Jacoby and Swartz (see Table 2).[13]

Tuberculosis was a diagnosis in at least one patient in 32 of the 35 series. Of the three series in which tuberculosis was not a diagnosis, one was a study from the 1930s.[2] In this article, Kinter and Rowntree make an impassioned point that tuberculosis is too often the mistaken diagnosis in patients with FUO. The other two series were relatively small (22 and 25 patients).[22,30]

In all, tuberculosis accounted for 214 (7.9%) of the diagnoses in the 2706 patients with adequate information (median 8%, range 0–42%). The rate was stable for the nine studies performed before the Petersdorf and Beeson article (7.7%) (see Table 1) and in the 20 adult series since (8.2%) (see Table 2). Among series conforming to the Petersdorf-Beeson definition, tuberculosis was more common in the non-US series (10.2%) than in the US series (5.3%) (see Table 2). Among specific populations, tuberculosis was responsible for FUO in 16.7% of patients with acquired immunodeficiency syndrome (AIDS), 9.5% of elderly patients, and 2.9% of pediatric patients (see Table 3). In four series from community hospitals, the rate was 5.9%, including 3.5% of cases reported from American community hospitals (see Table 2).[22,23,27,29]

In series involving 1366 patients, information concerning site of tuberculosis was available. Of these, 98 (7.2%) were diagnosed with tuberculosis, including extrapulmonary tuberculosis in 66 patients (4.8%) and pulmonary tuberculosis in 32 (2.3%). All cases of tuberculosis in the series focusing on the elderly were extrapulmonary.[33,34]

DISCUSSION

Fever of unknown origin is a classic syndrome long beloved by teachers and students, for the differential diagnosis is vast and traverses all of internal medicine. Mastering the approach to diagnosis remains a challenge in an ever-changing world of radiologic, serologic, and microbiologic advances. The syndrome of FUO has spawned at least the 37 studies included here, numerous additional reviews,[38–40] and a handful of less memorable other acronyms: PUO (pyrexia of unknown origin) was suggested by early authors,[3] but not surprisingly, rapidly fell into disuse. Similarly, the equally problematic FOO (fever of obscure origin) briefly held sway,[6–8,11] but finally yielded to the now ubiquitous FUO, which may refer to fevers of unexplained,[10] undetermined,[13] unknown,[16] or uncertain[32] origin.

As this review demonstrates, tuberculosis continues to be the cause of FUO in a significant number of patients, regardless of decade of study, continent, type of hospital, or underlying disease. Not surprisingly, extrapulmonary tuberculosis accounted for twice as many cases as pulmonary tuberculosis (about 5% of all cases), again emphasizing how exasperatingly difficult it may be to establish the diagnosis of extrapulmonary tuberculosis in certain patients. Rates were higher among AIDS patients, the elderly, in series reported from referral hospitals, and in non-US series.

Table 2. Reported Studies Utilizing the Petersdorf-Beeson Definition (n = 20)

Author	Study Location	Period	Total Cases	Diagnosis %*				Tuberculosis†	
				Inf	CA	CVD	Unk	Number (%)	Type
Petersdorf & Beeson[10]	New Haven	1952–57	100	36	19	15	7	11 (11)	4 P 7 EP
Sheon & Van Ommen[11]	Cleveland	1959–60	60	22	17	13	38	3 (5)	2 P 1 EP
Lascurain & Perez-Padilla[12]	Mexico City	1951–70	65	N/A	N/A	N/A	N/A	8 (12)	N/A N/A
Jacoby & Swartz[13]	Boston	1957–71	128‡	40	20	15	5-8	N/A	N/A N/A
Deal[14]	Gainesville	1960s	34	35	21	15	21	4 (12)	2 P 2 EP
Eyckmans et al[15]	Leuven, BLG	1965–72	80	34	19	9	13	7 (9)	N/A N/A
Barbado et al[16]	Madrid	1968–81	134	31	18	13	21	15 (11)	N/A N/A
Howard et al[17]	Temple, TX	1969–71	100	37	31	19	5	3 (3)	0 P 3 EP
Aduan et al[18]	NIH	16 y	222	8	11	15	29	N/A	N/A N/A
Larson et al[19]	Seattle	1970–80	105	30	31	9	12	4 (4)	0 P 4 EP
Arriaga et al[20]	Mexico City	1971–77	55	N/A	N/A	N/A	N/A	8 (15)	N/A N/A
Hassan & Farid[21]	Cairo	1971–73	129	60	14	10	12	21 (16)	N/A N/A
Fiala et al[22]	Los Angeles§	1976–77	22	64	18	0	0	0 (0)	0 P 0 EP
Gleckman et al[23]	Boston§	1970s	34	21	9	9	35	2 (6)	0 P 2 EP
Smith[24]	Dallas VAH	1979–85	80	50	15	1	9	3 (4)	N/A N/A
Lotholary et al[25]	Paris	1980–88	103	35	20	19	17	11 (11)	5 P 6 EP
Knockaert et al[26]	Leuven, BLG	1980–89	199	23	7	21	26	10 (5)	N/A N/A
Kazanjian[27]	Rhode Island§	1984–90	86	33	24	16	9	3 (3)	1 P 2 EP
Ponce-de-Leon-Rosales et al[28]	Mexico City	1988–93	77	N/A	N/A	N/A	N/A	6 (8)	N/A N/A
Shoji et al[29]	Shin'etsu, Jpn§	1986–92	80	54	9	16	18	8 (10)	5 P 3 EP

*Does not include patients with "Other" diagnoses (e.g., drug fever, factitious fever, pulmonary embolus, etc.); †included in "Infection" diagnosis group (P = pulmonary; EP = extrapulmonary); ‡percentages apparently include both 128 cases seen by authors and a literature review; §community hospital-based study.
Inf = infection; CA = cancer; CVD = collagen vascular disease, Unk = unknown; N/A = not available.

Many reports on FUO through the years have made the nostalgic point that FUO was somehow "not what it used to be."[24] The current review suggests otherwise: certainly, improved diagnostic techniques and the ready availability of more serologic tests and radiologic studies have had a major impact in what finally is diagnosed, as noted by Larson et al.[19] However, among the 19 series in adults that utilized a standard definition, infection accounted for 37% of diagnoses, cancer 15%, and collagen vascular disease 10%, rates similar to those reported in 1973.[13] Thus, although specific types of cancer and infection may differ in recent series versus those from the 1950s, the overall rates of the Big Three are the same: infection is about twice as common as cancer. This is important to consider when coordinating the workup of the patient with FUO. Interestingly, the spectrum of etiologies causing FUO in the horse is similar to that seen in man.[41] In one series of 63 cases of equine FUO, 43% were caused by infections (including 1 case of tuberculosis), 22% by neoplastic diseases, and at least 6% by "immune-mediated diseases."

The topic of fever and FUO has been addressed by many giants in the field of infectious disease, including Petersdorf, Beeson, Wolff, and Weinstein. In 1956, another of these giants, Ivan Bennett, noted "there is little to be gained by reviewing typical 'textbook' descriptions of diseases producing fever" since common diseases presenting uncommonly accounted for the majority of diagnoses.[42] The persistence of *M. tuberculosis* as the cause of FUO through the decades and across the continents certainly confirms this notion. For, after all of these years, through countless "revolutions" in diagnostic technique, ranging from fine-needle aspiration, radiometric culture techniques, computer-based radiologic scans, tuberculostearic acid assays, and most recently, molecular analysis by genetic probe or polymerase chain reaction, tuberculosis has continued to bedevil the physician confronted with a patient who has persistent fever. Based

Table 3. Series Reported in Specific Populations (n = 8)

Author	Study Population	Hospital Location	Study Period	Total Cases	Diagnosis %*				Tuberculosis†	
					Inf	CA	CVD	Unk	Number (%)	Type
Sepkowitz et al[30]	AIDS	New York	1988–90	25	60	16	0	16	0 (0)	0 P 0 EP
Bissuel et al[31]	AIDS	Paris	1989–91	57	72	7	0	14	10 (18)	N/A N/A
Miralles et al[32]	AIDS	Madrid	1991–92	50	82	4	0	12	21 (42)	N/A N/A
Esposito & Gleckman[33]	Elderly	Literature‡	1961–78	111	37	23	25	5	9 (8)	0 P 9 EP
Knockaert et al[34]	Elderly§	Leuven, BLG	1980–89	47	25	13	32	13	6 (13)	0 P 6 EP
McClung[35]	Pediatric	Wisconsin	1959–69	99	29	8	11	21	2 (2)	0 P 2 EP
Pizzo et al[36]	Pediatric	Boston	1966–72	100	52	6	20	12	1 (1)	N/A N/A
Chantada et al[37]	Pediatric	Argentina	1987–91	113	36	10	13	19	6 (5)	N/A N/A

*Does not include patients with "Other" diagnoses (e.g., drug fever, factitious fever, pulmonary embolus, etc.); †included in "Infection" diagnosis group (P = pulmonary; EP = extrapulmonary); ‡literature review; §included in 199 patients reported by Knockaert et al.[26]
Inf = infection; CA = cancer; CVD = collagen vascular disease; Unk = unknown; N/A = not available.

on this review, institution of a trial of empirical antituberculous therapy in any patient with FUO and no evident diagnosis after the first set of diagnostic procedures deserves strong consideration.

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